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Effect of Vitamin K2 on Postural Sway in Older People Who Fall: A Randomized Controlled Trial

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OBJECTIVES: Vitamin K is thought to be involved in both bone health and maintenance of neuromuscular function. We tested the effect of vitamin K2 supplementation on postural sway, falls, healthcare costs, and indices of physical function in older people at risk of falls.

DESIGN: Parallel-group double-blind randomized placebo-controlled trial.

SETTING: Fourteen primary care practices in Scotland, UK.

PARTICIPANTS: A total of 95 community-dwelling participants aged 65 and older with at least two falls, or one injurious fall, in the previous year.

INTERVENTION: Once/day placebo, 200 µg or 400 µg of oral vitamin K2 for 1 year.

MEASUREMENTS: The primary outcome was anteroposterior sway measured using sway plates at 12 months, adjusted for baseline. Secondary outcomes included the Short Physical Performance Battery, Berg Balance Scale, Timed Up & Go Test, quality of life, health and social care costs, falls, and adverse events.

RESULTS: Mean participant age was 75 (standard deviation [SD] = 7) years. Overall, 58 of 95 (61%) were female; 77 of

95 (81%) attended the 12-month visit. No significant effect of either vitamin K2 dose was seen on the primary outcome of anteroposterior sway (200 µg vs placebo: $-.19$ cm [95% confidence interval [CI] $-.68$ to $.30$; $P = .44$]; 400 µg vs placebo: $.17$ cm [95% CI $-.33$ to $.66$; $P = .50$]; or 400 µg vs 200 µg: $.36$ cm [95% CI $-.11$ to $.83$; $P = .14$]). Adjusted falls rates were similar in each group. No significant treatment effects were seen for other measures of sway or secondary outcomes. Costs were higher in both vitamin K2 arms than in the placebo arm.

CONCLUSION: Oral vitamin K2 supplementation did not improve postural sway or physical function in older people at risk of falls. *J Am Geriatr Soc* 00:1-6, 2019.

Key words: falls; vitamin K; postural sway; health economic analysis; recruitment

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Current evidence suggests that multifactorial falls interventions (combining strength and balance training, home environment modification, calcium and vitamin D supplementation, cataract extraction, and medication review) reduce falls in selected patients,¹ but the magnitude of effect is modest. Furthermore, such interventions are expensive,² labor intensive, and appear less successful when applied to a general older population^{3,4} than when applied to more highly selected groups of at-risk individuals referred to falls clinics. New simple and inexpensive ways of reducing falls in the wider population of older people are therefore needed.

Vitamin K is an essential cofactor for gamma carboxylation, required for the effective function of a range of proteins⁵ including those involved in bone remodeling, vascular calcification, glucose handling, inflammation, and neuromuscular function.⁶⁻¹² Low levels of dietary vitamin K intake are very common and associated with a higher risk of cardiovascular disease and osteoporosis.^{13,14}

In our previous work, a nonsignificant improvement in postural sway was seen with 6 months of once/day supplementation

with 100 µg vitamin K2 in participants aged 70 and older with vascular disease.¹⁵ Before conducting a large trial to evaluate whether vitamin K supplementation can reduce falls in older people at high risk, it is necessary to test which dose of vitamin K is effective (using a surrogate marker of falls risk) and to test whether recruitment to such a trial is feasible. The aims of this trial were therefore first to establish the optimum vitamin K dose to improve postural sway in older people, second to test recruitment strategy and likely effect size, and third to conduct preliminary health economic analyses to inform the design of future large multicenter trials of vitamin K to reduce falls in at-risk older people.

METHODS

Trial Design

This was a randomized double-blind parallel-group placebo-controlled trial. Ethics approval was obtained from East of Scotland Research Ethics committee (approval number 15/ES/0197), and the trial was registered at <http://isrctn.com> (ISRCTN18436190). Written informed consent was obtained from all participants at the screening visit.

Population and Recruitment

We recruited community-dwelling participants aged 65 and older with either two or more falls in the previous 12 months, or at least one fall resulting in hospitalization in the last 12 months. Exclusion criteria were an inability to give written informed consent; unable to stand without human assistance; atrial fibrillation (because this group should usually be taking warfarin); taking warfarin or other coumadin derivatives; taking more than 100 µg vitamin K supplement per day; known contraindication to vitamin K; currently enrolled in, or within 30 days of completing another trial; currently undertaking physiotherapy or another time-limited supervised nonpharmacologic intervention to reduce falls risk; and intolerance to soy products. All participants were recruited via primary care from three Health Board areas (Tayside, Grampian, and Fife). Telephone prescreening was conducted, and those eligible at this stage were invited to a combined screening and baseline visit.

Intervention and Comparator

Matching tablets containing either 200 µg vitamin K2 (MK7 subtype), 400 µg vitamin K2 (MK7 subtype), or placebo were manufactured and bottled by Legosan AB (Kumla, Sweden) and distributed to sites by Tayside Pharmaceuticals (Dundee, Scotland). The trial product was provided in identical bottles with a unique trial identifier on each bottle to ensure masking to participants, clinicians, and researchers. Participants were asked to take one tablet each day for the 12 months of the trial. No clear evidence exists to favor vitamin K1 or K2, or to favor a particular subtype of vitamin K2. However, MK7 was the subtype used in our previous trial that suggested possible benefit on postural sway.¹⁵ Thus this subtype was selected for use in the current trial but at higher doses than we used previously.

Randomization and Allocation Concealment

Randomization was performed in a 1:1:1 ratio by an online-based randomization system, run by the Health Informatics Centre, University of Dundee, to ensure allocation concealment. A minimization algorithm with a small random element was used to ensure balance across recruitment centers and key baseline measures. Minimization factors were trial center (Tayside, Grampian, or Fife), age (>80 or ≤80 y), and baseline anteroposterior (AP) sway (>3 cm or ≤3 cm).

Outcomes

The primary outcome was the between-group difference in AP sway at 12 months, measured using the AMTI AccuSway sway platform (AMTI, Watertown, MA, USA). Sway was measured with participants standing with feet together on the platform; three 30-second runs were performed with eyes open, followed by three 30-second runs with eyes closed. Sampling rate was 100 Hz, and proprietary software (AMTI Balance Clinic) was used to derive the outcome measures from raw center of pressure data. The mean value of each set of three runs was taken as the outcome measure. AP sway was previously shown to predict future falls in a range of populations.¹⁶⁻¹⁸ The secondary outcomes were other markers of postural sway (mediolateral sway, 95% ellipse, total path length) compared between groups at 6 and 12 months; Berg Balance Scale,¹⁹ the Short Physical Performance Battery,²⁰ Timed Up & Go Test,²¹ falls frequency collected using monthly falls diaries,²² and desphospho-undecarboxylated matrix Gla protein (dp-ucMGP) levels as a measure of the biological effect of vitamin K.²³ The dp-ucMGP was measured using a semi-commercial enzyme-linked immunosorbent assay by VitaK (Maastricht, Netherlands).²⁴ Office blood pressure was measured using an OMRON HEM-705 oscillometric device (OMRON). Participants were rested in a supine position for a minimum of 5 minutes, supine blood pressure was measured three times, and the mean of the second and third readings was used. Postural drop in blood pressure was measured as the largest drop between supine blood pressure and standing blood pressure measured immediately on standing, at 1 minute, and 3 minutes. We also collected health and social care utilization at each visit, and quality of life using the EuroQoL EQ5D-5 L and the Investigating Choice Experiments for the preferences of older people Capability Tool for Older People (ICECAP-O) tools.^{25,26} Adherence was measured by tablet count, comparing the number returned with the number expected to be returned at each study visit. All assessments were conducted by research nurses masked to treatment allocation.

Analysis

All analyses were conducted according to a prespecified statistical analysis plan, using SPSS software v.22 (IBM, Armonk, NY, USA). A two-sided *P* value <.015 was taken as significant for all analyses. Details of the analysis and sample size calculations are provided in Supplementary Material S1.

RESULTS

We sent study information to 4145 individuals identified from screening 14 primary care practices (6 in Tayside, 4 in Grampian, and 4 in Fife). A total of 444 expressed interest in the trial, of whom 99 attended a screening visit and 95 were randomized between June 28, 2016, and July 4, 2017. Baseline details of those randomized are given in Table 1; Supplementary Material S1 shows the Consolidated Standards of Reporting Trials diagram for participant flow through the trial. No significant difference in adherence was found between groups: 90% (SD = 20) in the 200 µg vitamin K group, 82% (SD = 27) in the 400 µg vitamin K group, and 88% (SD = 33) in the placebo group ($P > .05$ for all comparisons).

Figure 1 and Table 2 show the primary outcome results. No significant differences in AP sway were seen between groups at 12 months, either adjusted for baseline or adjusted for minimization variables. Table 2 and Supplementary Material S1 show the secondary outcomes. No significant differences were seen between groups for other measures of sway, for blood pressure, or for measures of physical performance. Dp-ucMGP levels were significantly lower, however, in the 200 µg and 400 µg vitamin K2 groups than in the placebo group, confirming that vitamin K was producing the expected dose-dependent effect on this marker of vitamin K biological activity. Supplementary Material S1 contains the results of falls analyses. The treatment groups did not show a statistically significantly different falls

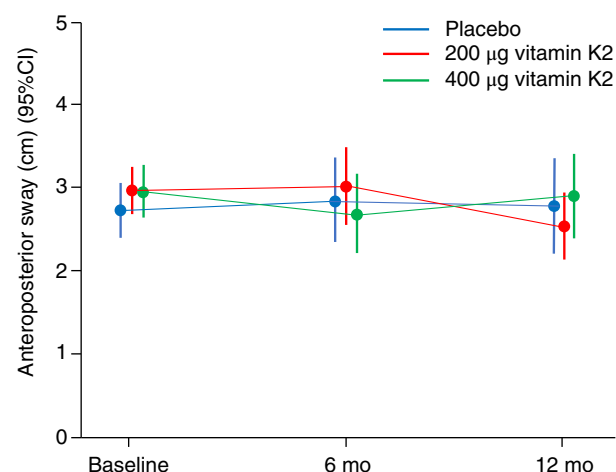


Figure 1. Anteroposterior sway at each time point by treatment group. CI, confidence interval.

rate to placebo, although falls rates were higher in the 200-µg arm. Time to first fall was also not significantly different from placebo in the treatment groups. There were more adverse events in the 200-µg arm than in the placebo or 400-µg arms as shown in Supplementary Material S1. This was driven by a slightly higher rate of gastrointestinal adverse events and a higher injury rate, paralleling the higher falls rate seen in the 200-µg arm.

Table 1. Baseline Characteristics

	Placebo (n = 32)	Vitamin K 200 µg (n = 32)	Vitamin K 400 µg (n = 31)
Mean age, y (SD)	75.0 (6.9)	74.7 (7.4)	75.1 (6.5)
Female sex (%)	18 (56)	21 (66)	19 (61)
Median number of falls in last year (IQR)	3 (2-7)	3 (2-6)	3 (2-4)
Uses walking aid (%)	21 (66)	15 (47)	12 (39)
Previous myocardial infarction (%)	2 (6)	1 (3)	1 (3)
Chronic heart failure (%)	0 (0)	1 (3)	0 (0)
Parkinsonian syndrome (%)	0 (0)	0 (0)	0 (0)
Previous stroke (%)	2 (6)	2 (6)	3 (10)
Hypertension (%)	17 (53)	15 (47)	18 (58)
Diabetes mellitus (%)	6 (19)	1 (3)*	8 (26)
Peripheral neuropathy (%)	4 (13)	1 (3)	2 (6)
Previous fragility fracture (%)	8 (25)	14 (44)	12 (39)
Osteoarthritis (%)	15 (47)	19 (59)	18 (58)
Chronic obstructive pulmonary disease (%)	4 (13)	7 (22)	6 (19)
Cataracts (%)	9 (28)	15 (47)	12 (39)
Retinopathy (%)	2 (6)	1 (3)	3 (10)
Median no. of medications (IQR)	5 (4-8)	6 (3-10)	6 (4-9)
ACEi/ARB (%)	14 (44)	12 (38)	12 (39)
Other antihypertensive or antianginal (%)	13 (41)	14 (44)	15 (48)
Vitamin D or analog (%)	4 (13)	12 (38)*	12 (39)*
Bisphosphonate (%)	1 (3)	5 (16)	5 (16)
Antidepressant (%)	8 (25)	8 (25)	7 (23)
Hypnotic (%)	5 (16)	0 (0)*	1 (3)
Opioid (%)	13 (41)	10 (31)	8 (26)
Mean body mass index, kg/m ² (SD)	29.7 (4.7)	29.4 (5.1)	30.8 (7.9)
Anteroposterior sway, cm (SD)	2.74 (1.01)	2.95 (.88)	2.93 (1.21)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range; SD, standard deviation.

* $P < .05$ compared with placebo.

Table 2. Anteroposterior Sway and Physical Performance Measures

		Baseline	6 mo	12 mo
Unadjusted anteroposterior sway, cm (SD)	Placebo	2.74 (1.01)	2.84 (1.35)	2.75 (1.38)
	Vitamin K 200 µg	2.95 (.88)	3.01 (1.33)	2.51 (1.02)
	Vitamin K 400 µg	2.93 (1.21)	2.67 (1.22)	2.88 (1.20)
	Treatment effect at 12 mo, cm (95% CI)			p
Adjusted for baseline	200 µg vs placebo	-.19 (-.68 to .30)		.44
	400 µg vs placebo	.17 (-.33 to .66)		.50
	200 µg vs 400 µg	.36 (-.11 to .83)		.14
Fully adjusted ^a	200 µg vs placebo	-.09 (-.53 to .35)		.69
	400 µg vs placebo	.19 (-.25 to .63)		.40
	200 µg vs 400 µg	.28 (-.15 to .70)		.20
Multiple imputation ^a	200 µg vs placebo	-.20 (-.66 to .26)		.39
	400 µg vs placebo	.04 (-.44 to .51)		.88
	200 µg vs 400 µg	.24 (-.22 to .67)		.31
Repeated measures ^a	200 µg vs placebo	-.07 (-.43 to .30)		.72
	400 µg vs placebo	-.08 (-.44 to .28)		.66
	200 µg vs 400 µg	-.02 (-.37 to .34)		.93
		Baseline	6 mo	12 mo
Unadjusted SPPB (mean, SD)	Placebo	7.7 (2.3)	8.0 (2.7)	7.9 (3.0)
	Vitamin K 200 µg	7.4 (2.6)	7.8 (2.7)	7.8 (2.7)
	Vitamin K 400 µg	7.1 (2.7)	7.2 (2.8)	6.7 (3.1)
		Treatment effect at 12 mo		P
SPPB treatment effect ^a (95% CI)	200 µg vs placebo	-.2 (-1.1 to .7)		.63
	400 µg vs placebo	-.4 (-1.3 to .5)		.37
	200 µg vs 400 µg	-.2 (-1.1 to .7)		.66
		Baseline	6 mo	12 mo
Unadjusted Timed Up & Go (median, IQR)	Placebo	12.9 [9.7-17.1]	9.9 [8.5-16.2]	11.2 [9.1-17.2]
	Vitamin K 200 µg	14.2 [9.2-21.3]	11.7 [8.4-18.1]	12.5 [8.9-19.0]
	Vitamin K 400 µg	14.1 [9.4-20.4]	12.9 [8.4-17.9]	13.3 [9.6-18.7]
		Treatment effect at 12 mo		P
Log ₁₀ Timed Up & Go Test treatment effect ^a (95% CI)	200 µg vs placebo	.02 (-.03 to .07)		.44
	400 µg vs placebo	.03 (-.02 to .09)		.23
	200 µg vs 400 µg	.01 (-.04 to .06)		.64
		Baseline	6 mo	12 mo
Unadjusted Berg Balance Scale (median, IQR)	Placebo	50 [45-53]	51 [38-53]	52 [41-54]
	Vitamin K 200 µg	48 [42-53]	52 [46-54]	50 [47-54]
	Vitamin K 400 µg	48 [44-54]	47 [42-54]	49 [40-54]
		Treatment effect at 12 mo		P
Log ₁₀ Berg Balance Scale treatment effect ^a (95% CI)	200 µg vs placebo	.00 (-.00 to .02)		.31
	400 µg vs placebo	-.00 (-.02 to .01)		.80
	200 µg vs 400 µg	-.01 (-.03 to .00)		.20

Abbreviation: CI, confidence interval; IQR, interquartile range; SD, standard deviation; SPPB, Short Physical Performance Battery.

^aAdjusted for age, sex, baseline anteroposterior sway, and trial center.

Costs were lowest over 1 year among participants randomized to the placebo group (mean cost = £764 per participant). Costs were lower among participants in the low-dose vitamin K2 group, relative to high-dose vitamin K2 (£896-£902 vs £1033-£1044). Supplementary Material S1 combines the data just cited to show the incremental costs and quality-adjusted life years for the 200 µg and 400 µg vitamin K2 arms compared with placebo. Neither dose of vitamin K2 produced any improvement relative to placebo. Supplementary Material S1 shows the Expected Value of Sample Information graph. Based on the assumptions used, the optimal sample size for the most cost-effective future trial would be 131 participants per group, but such a trial would remain cost effective up to a sample size of 1100 per group.

DISCUSSION

There are a number of possible explanations for the lack of observed benefit of vitamin K supplementation that merit consideration. Adherence was good, and the Dp-ucMGP results confirm that the vitamin K had a measurable biological effect, but it is still possible that an even larger dose is required to improve sway or that vitamin K has to be given for longer to achieve an effect. The study population was at risk of falls, as shown by the average of 1.7 falls per participant during the trial. However, postural sway was relatively low in the trial population. Thus a ceiling effect may have limited the ability of the trial interventions to produce a measurable change. A more challenging balance task than standing on a firm level surface may be required to allow

any benefit of the intervention to be observed in this participant group. Although previous studies found that many older people have low dietary vitamin K intakes, we did not examine dietary intake of vitamin K via food diaries in this trial, and so we cannot be sure if the trial population had particularly low vitamin K intakes. However, the fact that both 200- μ g and 400- μ g doses of vitamin K significantly lowered dp-ucMGP levels suggests that participants were not vitamin K replete at baseline.

One previous trial examined the effect of vitamin K supplementation on postural sway; this trial did not find a significant benefit of lower dose vitamin K supplementation on this outcome.¹⁵ Previous trials suggest, but do not establish conclusively, a beneficial effect on vascular health of vitamin K. A recent meta-analysis⁷ showed statistically significant improvements in vascular calcification but not in vascular stiffness, arguably a more important functional measure of vascular health and one that has been linked to orthostatic hypotension, a potential mediator of falls. It is possible that an even longer duration of therapy is required to produce benefit from vitamin K supplementation; one trial in postmenopausal women did not find significant benefit before the third year of supplementation.²⁷

Our trial has a number of strengths. The groups were balanced at baseline, the trial recruited participants at an elevated risk of falls, and both retention and intervention adherence were good. The involvement of multiple recruitment and assessment center improves the generalizability of our results. A number of additional limitations require comment. Effects in people with different ethnicity or diet cannot be ascertained because the trial population were overwhelmingly white, and dietary information was not collected. The trial was not powered to detect a difference in falls rates, and thus an effect on falls rates cannot be excluded; such an effect could be mediated by mechanisms other than improvements in postural sway or orthostatic hypotension that we did not measure in this trial.

It is possible that populations at higher risk (eg, those in nursing homes, falls clinics, or those with very low vitamin K intake) could still potentially benefit, and future research could usefully target these groups. At present, however, insufficient evidence exists to recommend use of vitamin K supplementation in community-dwelling older adults at risk of falls.

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Conflicts of Interest: None to declare.

Author Contributions: *Study design:* Witham, Price, Band, Fulton, Clarke, Donnan, McNamee, Cvorro, and Soiza. *Study management:* All authors. *Analysis of results:* Witham, Hannah, Donnan, and McNamee. *Interpretation of results:* All authors. *Drafting of manuscript:* Witham and McNamee. *Critical revision of manuscript:* All authors.

Sponsor's Role: The sponsor approved the protocol, but the design, results analysis, and manuscript drafting were all performed independently with no input from the sponsor (Tayside Academic Sciences Centre, a joint enterprise between University of Dundee and NHS Tayside)

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Material S1: Supplementary methods (analysis and sample size calculation), results tables and figures